

HCDT: an integrated highly confident drug–target resource

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Abstract

Drug–target association plays an important role in drug discovery, drug repositioning, drug synergy prediction, etc. Currently, a lot of drug-related databases, such as DrugBank and BindingDB, have emerged. However, these databases are separate, incomplete and non-uniform with different criteria. Here, we integrated eight drug-related databases; collected, filtered and supplemented drugs, target genes and experimentally validated (highly confident) associations and built a highly confident drug–target (HCDT: <http://hainmu-biobigdata.com/hcdt>) database. HCDT database includes 500 681 HCDT associations between 299 458 drugs and 5618 target genes. Compared to individual databases, HCDT database contains 1.1 to 254.2 times drugs, 1.8–5.5 times target genes and 1.4–27.7 times drug–target associations. It is normative, publicly available and easy for searching, browsing and downloading. Together with multi-omics data, it will be a good resource in analyzing the drug functional mechanism, mining drug-related biological pathways, predicting drug synergy, etc.

Database URL: <http://hainmu-biobigdata.com/hcdt>

Introduction

Drug discovery is a time-consuming, costly and risky process (1). According to a report published in 2021, the average time to develop a new drug from clinical trials to market was 7.5 years (2). With clinical development proceeding from Phase 1 to Phases 2 and 3, the average cost per study increased for all therapeutic areas. However, the average success rate for developing new drugs was only 2.01% (2, 3). The annual investment in drug development has gradually increased, even while the number of Food and Drug Administration-approved drugs has been declining since 1995 (4). Between 2009 and 2018, the median cost of developing a new drug was \$985 million, while the average sum totaled \$1.3 billion. In all therapeutic areas, oncology and immunomodulatory drugs were the most expensive to develop, coming in at a median of \$2.8 billion and a mean of \$4.5 billion (5). The cost of new drug development will continue to grow. Hence, it is urgent to find a new strategy to discover drugs (1).

Drug repositioning (6), also known as drug repurposing, uses the molecular structure, indications and adverse effects of a known drug to develop new functions beyond the drug testing, safety review and clinical phases of the traditional drug development model. It reduces costs and time with low risk (1, 7).

Using the structure, properties and target interactions to predict new functions of drugs is a key step in drug repositioning, and a key point is to know and understand the relationship between drugs and targets (8, 9). The association between a drug and target gene can be determined by *in vitro* and *in vivo* studies, and a lot of drug-related databases have been constructed, such as ChEMBL (10), DrugBank (11) and DtoPdb (12). A variety of computational methods to predict drug–target association have been proposed, such as data mining (13), machine learning methods (14, 15), neural networks (13, 16) and collaborative matrix decomposition methods (9). Key information used in these methods is the known experimentally confirmed drug–target associations.

In some drug-related databases, the associations between drugs and targets have been experimentally validated, such as DrugBank, KEGG (17) and PubChem (18). However, in some databases, in addition to experimentally confirmed drug–target association, there are also computational predicted drug–target associations, such as BindingDB (19), STITCH (20) and ChEMBL. We can get quite different drug–target associations when using different predicting methods or thresholds. Therefore, experimentally validated drug–target associations are more confident than the predicted ones and much useful in drug repositioning and other studies.

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Table 1. Database information and criteria

Database	Drug label				Gene label				Criteria	
	SMILES	IUPAC name	Inch	ATC codes	Binding affinity	Gene symbol	Entrez ID	Ensembl ID		UniProt ID
BindingDB	✓		✓		✓				✓	Including criteria (i) binding affinity, including at least one of K_i , K_d , IC_{50} or $EC_{50} \leq 10 \mu M$; (ii) the presence of UniProt ID representation of the protein and (iii) the protein being tagged as ‘review’.
ChEMBL	✓	✓	✓	✓	✓			✓	✓	
GtoPdb	✓	✓	✓		✓	✓			✓	
PubChem	✓	✓	✓	✓	✓	✓			✓	
TTD	✓		✓		✓	✓			✓	
DGIdb	✓	✓				✓	✓			Fourteen of these experimentally validated database sources are screened for drug–target interactions and eight are excluded. See the details in Supplementary Table S1 .
DrugBank	✓	✓	✓	✓		✓		✓	✓	Interactions with no clear target information are excluded.
PharmGKB	✓	✓	✓	✓		✓		✓		Only the data marked as ‘associated’ are included.
CancerDR	✓					✓		✓		CancerDR database is excluded as it is mainly used for the study of drugs and sensitive cell lines, but lacks the information of the corresponding target effects.
STITCH	✓					✓				STITCH and SuperPred are excluded, as the majority of drug–target association are based on computational prediction, but not confirmed by biological experiments, which do not meet the high confident purpose of this study.
SuperPred	✓		✓		✓					
SIDER	✓			✓						SIDER database is excluded as it is used for the study of drug side effects but lacks target information.
KEGG	✓	✓	✓	✓		✓		✓	✓	KEGG is excluded, as the drug–target information is simply collected from ChEMBL, DrugBank and PubChem, without selection or integration.

The information in these databases varies a lot due to their different research purposes. SIDER and DrugBank focus on the drug structure and function, with less information on target genes (11, 21). DGIdb focuses more on drug–target associations without specific information on corresponding drugs and targets (12). STITCH and SuperPred focus on the prediction of new drug functions (20, 22). PharmGKB contains too little information on experimentally validated data, while BindingDB has too much information on predicted data to meet the data needs of researchers (19, 23). Meanwhile, there are different identifications for drugs and genes, and it makes extra burden for researchers when they acquire information from different databases.

Here, we used unified standards for drugs and target genes, integrated the experimentally validated drug–target associations in the current popular drug-related databases and constructed a highly confident drug–target (HCDT (<http://hainmu-biobigdata.com/hcdt>)) database.

Materials and methods

Data collection and processing

We have collected 13 commonly used drug databases: BindingDB, ChEMBL, DGIdb, DrugBank, GtoPdb, PharmGKB, PubChem, TTD (24), CancerDR (25), STITCH, SIDER, SuperPred and KEGG (see details in Table 1). The drug-related data are expected to contain simplified molecular input line entry system (SMILES), International Union of Pure and Applied Chemists (IUPAC) name, International Chemical Identifier (INCH), The Anatomical Therapeutic Chemical codes and binding affinity of the drug; for the gene data, it is guaranteed to contain one of the gene symbols, Entrez ID, Ensembl ID or UniProt ID, which can be mapped with the gene information in the HGNC database.

Five of these databases were excluded in the following steps: CancerDR database is mainly used for the study of drugs and sensitive cell lines but lacks the information of the corresponding target effects; in STITCH and SuperPred,

the majority of drug–target associations are based on computational prediction, but not confirmed by biological experiments, which do not meet the highly confident purpose of this study; SIDER database is used for the study of drug side effects but lacks target information; In KEGG, the drug–target information is simply collected from ChEMBL, DrugBank and PubChem, without selection or collation.

The left eight databases were selected as the original data sources for the HCDT database. To ensure the high confidence of drug–target associations, we used the following criteria: for databases with drug binding affinity information (BindingDB, ChEMBL, GtoPdb, PubChem and TTD), we retained only drug–target associations that met the following three criteria (22): (i) binding affinity, including at least one of K_1 , K_d , half maximal inhibitory concentration (IC_{50}) or half maximal effective concentration (EC_{50}) $\leq 10 \mu\text{M}$; (ii) the presence of UniProt ID representation of the protein and (iii) the protein being tagged as ‘review’. DGIdb is integrated by several databases. In the latest release of DGIdb 4.0 (26), we screened 14 databases for experimentally validated drug–target association and excluded three databases with drug–target prediction and five databases (ChEMBL, DrugBank, GtoPdb, PharmGKB and TTD) that had been collected separately (see the details in Supplementary Table S1). In PharmGKB, there were three types of drug–target relationships: ‘associated’, ‘not associated’ and ‘ambiguous’, and only the data marked as ‘associated’ were selected. All drug–target associations are validated by *in vivo* experiments and guaranteed to be of human origin but not of other species.

Drug classifications

There are various kinds of drug classifications in these databases. A drug may be marked as different types in different databases. For example, tisagenlecleucel (27), an immune agent for B-cell lymphoma, is marked as ‘antibody’ in ChEMBL and ‘biotech’ in BindingDB. There are about 268k drugs in BindingDB, which account for 89.5% of drugs in HCDT database. Therefore, we classified drugs based on BindingDB first and then referred other classifications in other databases. There are six drug types in BindingDB: small-molecule organic compounds (synthetic small molecule), synthetic products of biotechnology (Biotech), metabolites, oligomer and combination of drug pairs and unknown drug types that do not fall into the above five categories. For Biotech, there are subtypes such as protein, cell, enzyme, gene in ChEMBL, antibody in ChEMBL and GtoPdb. For oligomer, there are four subtypes, such as oligonucleotide, oligopeptide and oligosaccharide in ChEMBL and peptide in GtoPdb. There are also two special drug types in GtoPdb. For example, apigenina (28), a flavonoid, is shown as a natural product in ChEMBL and GtoPdb, but does not belong to any six types in BindingDB; nitric oxide, a selective pulmonary vasodilator used to treat various forms of pulmonary hypertension in order to improve oxygenation levels, is marked as inorganic in GtoPdb, but it does not belong to any six types in BindingDB. Finally, we got eight types of drugs (Figure 1).

For each drug, we use the label in BindingDB if a drug exists in BindingDB (for example, tisagenlecleucel is marked as ‘biotech’ as it is marked as ‘biotech’ in BindingDB); we match label in the original database to the corresponding BindingDB label if a drug does not exist in BindingDB, but

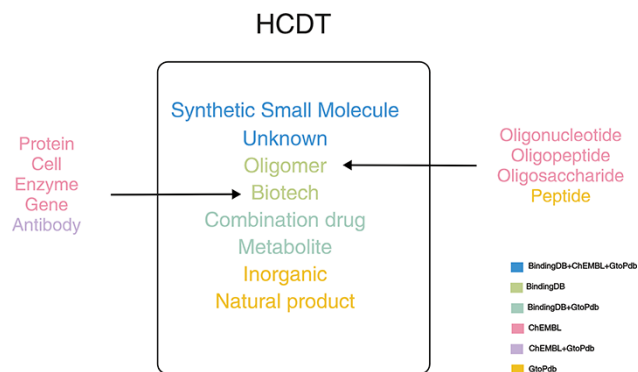


Figure 1. Drug classifications in HCDT database.

the labels can match [for example, MIPOMERSEN (29) is marked as ‘Oligomer’ as it is marked as ‘Oligonucleotide’ in ChEMBL]; we use label inorganic or natural product, if a drug belonged to these two types.

Gene types

Based on the HGNC database, genes are classified into four groups according to function (30): genes that encode proteins, genes that do not encode ribonucleic acid (RNA), pseudogenes that have no actual function and the remaining genes whose function is not yet clear. Then, they are further subdivided into a total of 24 subtypes based on their specific attached functional objects. The main type of protein-coding gene group is a collection of genes that can encode proteins; the non-coding RNA group is divided into 10 types according to the RNA type that can be transcribed and translated into sex chromosomes, long-stranded non-coding RNA, microRNA and small RNA; pseudogenes are non-functional residues formed during gene evolution and can be divided into three types: T-cell receptor pseudogenes, immunoglobulin pseudogenes and pseudogenes with unknown receptors; for the other 10 subtypes such as functional T-cell receptor genes, complex site component genes and endogenous retroviral genes, they make up the fourth group because the attachment object loci are still unclear.

Data integration

The SMILES information is used as the unique identifier (31) for drugs and then other features, such as IUPAC name (32), and synonyms are matched to the drugs. For genes, the gene symbol is used as the unique identifier and the HGNC database is used to supplement the information on UniProt ID, Entrez ID, gene type, location and Ensembl ID. The drug–target relationships in each database were then integrated based on SMILES and gene symbol.

Results

Data in HCDT database

In total, 299 458 drugs, 5618 genes and 500 681 pairs of associations were obtained in HCDT database (Table 2). BindingDB is the largest source of HCDT database.

Drug–target network

A drug–target network is constructed based on the drug–target association. The distribution of degrees for drug (the number of corresponding targets for a drug) is shown in Figure 2. A drug is associated an average 1.7 experimentally validated target genes, and 220 198 (73.53%) drugs are associated with only the target. Staurosporine (33), an adenosine triphosphate–competitive, non-selective protein kinase inhibitor, has up to 333 targets. Similarly, the distribution of degrees for target (the number of corresponding drugs for a target gene) is shown in Figure 3. A target gene is associated an average 89.1 drugs, and 1214 (21.61%) genes are associated with only one drug. HCRTR2 has 6435 related drugs, which is the largest number (34). The protein encoded by HCRTR2 is a G-protein coupled receptor (GPCR), and it is involved in encoding hypothalamic secretagogues that lend themselves to the regulation of appetite and sleep behavior. GPCRs are the largest family of membrane receptors that are targeted by approved drugs, and approximately 35% of approved drugs target GPCRs (35). The drugs associated with HCRTR2 can be divided into activators and inhibitors. The amide carbon group for the junction is present in the activator. The amide carbonyl of the linker forms a hydrogen bond with H350, whose sidechain also contacts the terminal 1,2,3-triazole moiety and the distal phenyl ring of the core, thereby stabilizing

the kinked conformation of HCRTR2. As for inhibitors, all antagonists occupy the bottom-most region of the central cavity, overlapping with the last three residues of HCRTR2 and the portion of a compound containing the sulfonamide and the amide-linked phenyltriazole (36). A list of hub drugs and targets is shown in Supplementary Table S2.

We take the top 5% of drugs and genes of degrees in the networks as hubs, where the drugs had at least four targets and the genes had at least 31 target drugs. Then, we compare the hubs between HCDT database and the eight individual databases. For genes, all hub genes in BindingDB and ChEMBL belong to HCDT database (Supplementary Figure S1A and B), which is because BindingDB and ChEMBL provide most drugs for HCDT database. Most hub genes (204/282) in HCDT database are hubs in these individual databases (Supplementary Figure S1I). For drugs, all or most hub drugs in seven individual databases except BindingDB are hubs in HCDT database (Supplementary Figure S2B–H), and about half (7305/13 400) of hub drugs in BindingDB are hubs in HCDT database (Supplementary Figure S2A). These results show that HCDT database is consistent with these individual databases and provides more information as an integrated database.

Table 2. Statistics on HCDT data sources

Database	Number of drugs	Number of targets	Number of associations
BindingDB	268 001	2293	357 695
ChEMBL	17 110	1018	42 571
DGIdb	10 025	2344	41 924
DrugBank	6393	3168	27 111
Gtopdb	8821	1766	18 352
PharmGKB	1178	1868	18 084
PubChem	11 049	3840	64 483
TTD	27 761	2510	56 048
HCDT database	299 458	5617	500 681

Drug and target classification

299 458 drugs were classified into eight types in HCDT database (Table 3). There are 268 722 synthetic small-molecule drugs, which is in line with the reality of drug design, where small organic compounds are mostly used in clinical drug development (37). There are only 156 inorganic drugs. Inorganic drugs have been identified as significant candidates for new cancer therapeutic modalities because of their biocompatibility, easy functionalization and fabrication, optical tunable characteristics and chemical stability. However, the problems of eliminating long-term toxicity from metals *in vivo* and transport of drug carriers have led to the still low number of inorganic drugs entering clinical usage (38, 39).

5618 target genes are classified into 11 subtypes in HCDT database (Table 4), and 5492 of them (97.8%) are

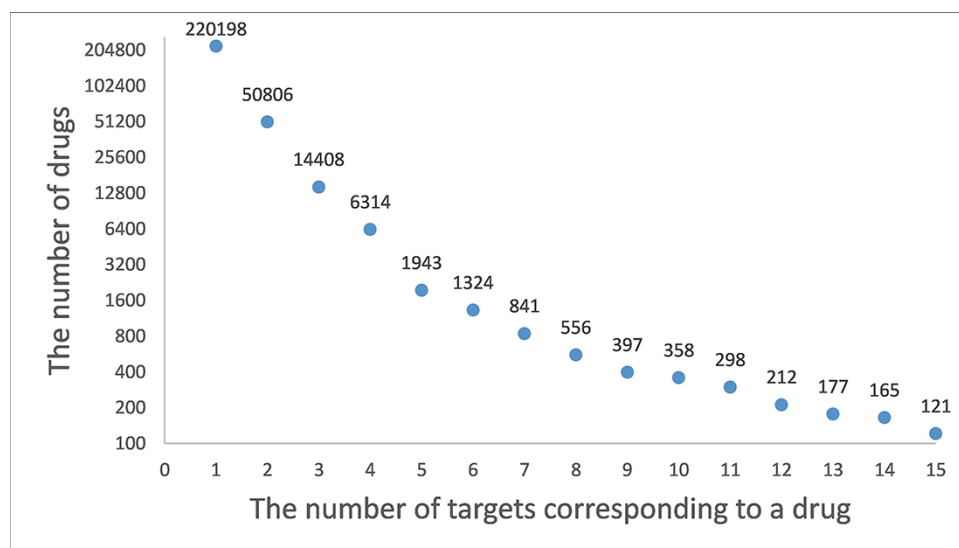


Figure 2. A frequency plot of the number of targets for a drug. The x-axis indicates the number of targets corresponding to a drug and the y-axis indicates the number of drugs. In this figure, only the drugs with less than 15 target genes are shown which account for 99.5% of the drugs.

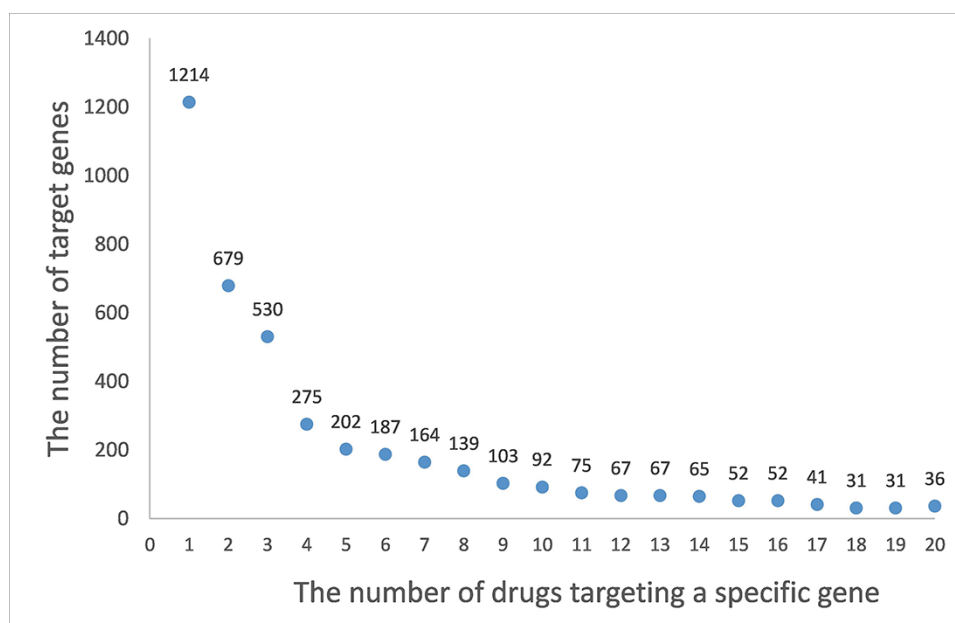


Figure 3. A frequency plot of the number of drugs targeting a specific gene. The x-axis indicates the number of drugs targeting a specific gene, and y-axis indicates the number of target genes. In this figure, only the genes with less than 20 related drugs are shown which account for 73% of the target genes.

Table 3. Drug statistics in HCDT database

Drug type	Number of drugs
Synthetic small molecule	268 722
Natural product-derived	18 864
Biotech	4978
Oligomer	2824
Metabolite	1778
Inorganic	156
Combination drug	439
Unknown	1697
Total	299 458

Table 4. Types of genes in HCDT database

Gene type	Number of genes
Gene with protein product	5492
Pseudogene	39
RNA, micro	28
Immunoglobulin gene	21
RNA, long non-coding	18
Complex locus constituent	9
T cell receptor gene	3
Readthrough	4
RNA, small nucleolar	2
RNA, misc	1
RNA, ribosomal	1
Total	5618

protein-coding genes. Different types of genes have different functional mechanisms in drug effect, and HCDT database could be used to analyze the potential mechanism for drugs.

Comparison with individual databases

HCDT database is an integrated normative database, and it includes as much information as possible for drugs and target

genes. For each drug, there are SMILES, PubChem Compound ID, IUPAC name, synonyms, INCH and drug type. For each gene, there are gene symbol, Ensembl ID, gene type, location, Entrez ID and UniPort ID. Not every information exists in these individual databases. For example, in ChEMBL, the target genes are represented by gene-encoded proteins, but not gene symbols; similarly, SMILES and IUPAC name information of some drugs in BindingDB are missing. Therefore, HCDT database is much convenient for researchers.

Compared to individual databases, HCDT database has a much greater volume. It contains 1.1–254.2 times drugs, 1.8–5.5 times target genes and 1.4–27.7 times drug–target associations. Among these databases, BindingDB is the largest data provider, which accounts for 89.50% of drugs, 40.82% of target genes and 71.44% of drug–target associations. For individual databases, there are different types of data information for drugs, targets and associations depending on the purpose of the study. For example, DrugBank lacks target structure information; DGIPdb has descriptions of associations but lacks drug-specific information; BindingDB has records of both drug and target information but is more complicated to operate and has a lot of prediction information. HCDT database combines the advantages of each database and complements the drug, target and association information.

In HCDT database, 399 429 (79.78%) drug–target associations came from only one raw database, most associations (99.21%) existed in less than four raw databases and only 48 associations were present in all eight databases (Figure 4). For example, amitriptyline is a commonly used antidepressant in various types of depression as well as in chronic pain (40). The association of amitriptyline with CACNA1C is only recorded in BindingDB, the association of amitriptyline with Potassium Voltage-Gated Channel Subfamily H Member 2 is recorded in BindingDB, DrugBank and PubChem and the

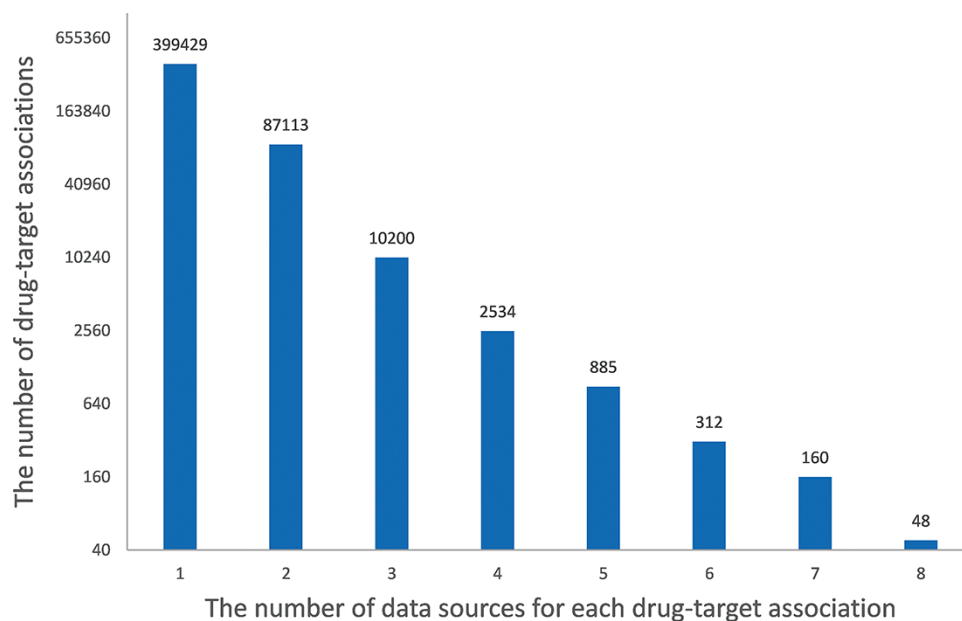


Figure 4. Histogram of the number of data sources for each drug–target association. The x-axis indicates the number of data sources for each drug–target association, and the y-axis indicates the number of drug–target associations.

association of amitriptyline with SLC6A4 is recorded in all eight databases. This indicates that the drug–target associations in each database are somewhat related but have some variability due to the different purposes of each database. Integration of these databases in HCDT database greatly improves the volume and credibility of drug–target associations.

Discussion

Drug–target association plays more and more roles in drug discovery, drug repositioning, drug synergy prediction, etc. HCDT database (<http://hainmu-biobigdata.com/hcdt>) is a publicly available resource for highly confident drug–target associations. The researchers can query drug–target associations via drugs or target genes and can download all the associations. HCDT database integrated eight databases and includes 500 681 highly confident (experimental verified) drug–target associations. It has the largest volume and has as much information as possible for drugs and target genes. Together with multi-omics data, it will be a good resource in analyzing the drug functional mechanism, mining drug-related biological pathway, predicting drug synergy, etc.

Supplementary data

Supplementary data are available at *Database* Online.

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Conflict of interest

The authors declare no conflict of interest.

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